Hyperthermia: New Thoughts on an Old Problem

Roger W. Hubbard, PhD
Lawrence E. Armstrong, PhD

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In brief: This article reviews the causes and treatment of the common heat illnesses—heat syncope, heat exhaustion, and exertional heatstroke. The authors discuss the effectiveness of cooling heatstroke victims in ice water vs water that has been cooled to a temperature of 15° C. The latter method is more practical and has been found as effective as cooling with ice water. The authors also present the energy depletion model, which shows the cycle that results in reduced exercise/heat tolerance and significant morbidity and mortality in victims of exercise-induced hyperthermia. This model predicts that cellular/metabolic processes and deficits operate for some time after hyperthermia has subsided with cooling.

The potential conductance of the vasculature (skin, 7 $L \cdot min^{-1}$; viscera, 3 $L \cdot min^{-1}$; and muscle, 65 to 70 $L \cdot min^{-1}$) is enormous and far exceeds the pumping capacity of the normal human heart (about 22 $L \cdot min^{-1}$).[1] Since the combined blood flow requirements of these vascular beds cannot be met in a person who is experiencing heat stress while exercising in an upright position, an inherent competition takes place between the mechanisms that maintain blood pressure and

Dr Hubbard is director and Dr Armstrong is a research physiologist, Heat Research Division, US Army Research Institute of Environmental Medicine, Natick, Massachusetts. Dr Hubbard is also an adjunct associate professor of pathology at Boston University School of Medicine and is a member of the American Physiological Society. Dr. Armstrong is a fellow of the American College of Sports Medicine. Dr Bracker is assistant clinical professor in the Department of Community and Family Medicine at the University of California, San Diego, School of Medicine. He is an editorial board member of THE PHYSICIAN AND SPORTSMEDICINE and a diplomate of the American Board of Family Practice.

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Some degree of heat illness may strike runners during warm weather. Affected athletes should stop activity and lie down; the body should be cooled and fluid/electrolyte deficits replaced.

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Table 1. Diagnosis and Treatment of the Most Common Heat Illnesses*

	Diagnosis	Treatment
Heat cramps	Associated with whole-body salt deficiency. Cramps occur in abdominal wall and large muscles of the extremities but differ from exertion-induced cramps: *entire muscle* not involved; cramp appears to wander because individual muscle bundles contract. Plasma Na^+ deficit; urine NaCl concentration from a trace to 3 gm/L; 51 mEq/L, with specific gravity > 1.016. Observed mostly in *unacclimatized individuals*.	Oral 0.1% saline solution (two 10-grain salt tablets in 1 L water) or IV 0.5-1.0 L normal saline solution IV solutions, used when symptoms include nausea and vomiting, bring rapid relief with no lasting sequelae.
Heat exhaustion	Inability to continue activity in the heat. Symptoms may include nausea, vomiting, irritability, headache, "heat sensations" on head and trunk, orthostatic changes, syncope, dyspnea, weakness, piloerection. T_{re} up to 39° C, depending on the physical activity that preceded overt illness and the point at which temperature was first recorded. Sweating is profuse. Mental function and thermoregulation are mildly impaired. Acclimatization reduces incidence of symptoms. There are three types of heat exhaustion; the first two involve peripheral vascular collapse: 1. Water depletion. Hypohydration, prominent thirst; cramps seldom seen; onset possible with a few hours of exercise. 2. Salt depletion. Prominent fatigue, cramps, vomiting, progressive weakness; thirst seldom observed; onset within 3-5 days. 3. Nonclassic exercise-induced. Tetany, carpopedal spasms, abdominal cramps, syncope, *respirator / alkalosis* (all induced by hyperventilation); absence of primary salt or water depletion; onset of overt symptoms is acute.	Type 1 and 2. Rest and cooling increase venous return to heart. Mixed salt/water depletion is usually seen. Replace water and electrolytes based on measures of serum Na^+, protein, BUN, Hct, pulse, BP, or orthostatic changes. After the duration of exercise and heat exposure and the amount of fluid intake are determined, water and electrolyte loss may be estimated as 1.5 L water and 2 gm NaCl per hour of continuous, moderate to heavy exercise. (Typical losses during a 4-hr work shift in harsh conditions are 6.0 L water and 8 gm NaCl.) *Type 3. Rest, cooling and rebreathing of expired air* The prognosis is best when mental acuity is not altered and when serum enzymes are not elevated. Immediate return to work/exercise is inadvisable, except in mildest cases; allow 24-48 hr for recovery.
Exertional heatstroke	Thermoregulatory failure. T_{re} of 39.4°-40.6° C or higher. Other symptoms include elevated serum enzymes (AST, ALT, LDH, CPK), hypotension, vomiting, diarrhea, coma, convulsions, and frank impairment of mental function and temperature regulation. Sweating may or may not be present. Onset may be rapid in patients who have been exercising.	A true medical emergency. Intubate patient if comatose or convulsing. If cardiovascular difficulties are severe or if peripheral blood flow is compromised, use conductive cooling by immersing the patient in ice water. Immersion therapy not only provides the fastest cooling rate when T_{re} is > 40.6° C, but also improves venous return and cardiac output via skin vasoconstriction and the effects of hydrostatic pressure. Seek a cooling rate of 0.15° C·min^{-1} until T_{re} reaches 37.88° C, then monitor. In most cases the T_{re} reaches 37.8° C within 30 min. Monitor T_{re} for rebound hyperthermia at regular intervals for 24-48 hr. Administer IV fluids judiciously (1.0-1.5 L); consider possible pulmonary edema. Analyze serum enzymes and coagulation factors for seven days. Monitor renal and acid-base status. Complications may include CNS damage, renal failure, rhabdomyolysis, DIC, and hepatic or myocardial necrosis. The prognosis is best when peak T_{re} is < 42.2° C, serum AST < 1,000 U/L in the first 24 hr, and duration of coma is > 2 hr. The mortality rate (10%-80%) is directly related to the duration and intensity of hyperthermia as well as to the speed and effectiveness of diagnosis and treatment.

*Abbreviations

ALT alanine aminotransferase
AST aspartate aminotransferase
BP blood pressure
BUN blood urea nitrogen
CNS central nervous system
CPK creatine phosphokinase
DIC disseminated intravascular coagulation
Hct hematocrit
IV intravenous, intravenously
LDH lactate dehydrogenase
T_{re} rectal temperature

those that maintain blood flow to support muscle metabolism and thermoregulation.

The regulation of these competing mechanisms is complex. For example, a rise in skin blood flow increases cutaneous venous volume, which not only enhances heat loss from the skin but also creates a reduction in effective central blood volume. It has long been held that a fall in blood pressure under these conditions is avoided because of a reduction in splanchnic and renal blood flow via increased splanchnic vasoconstriction. This attempt to maintain blood pressure at the expense of the liver, kidneys, and other organs seems to account for the high rate of hepatic and renal complications in exertional heatstroke.

Depending on the intensity and duration of exercise-induced hyperthermia, cardiovascular compensation begins to fail. At some point the affected individual ceases to work, or collapses with one of the characteristic heat illnesses, eg, heat syncope, heat exhaustion, or heatstroke; the condition is diagnosed and therapy initiated (table 1). Classic therapy addresses the basic physiologic causes of distress and matches the treatment with the stress; ie, have the patient cease activity, lay the patient down, cool the the patient's body, and replace fluid/electrolyte deficits.

Table 2. International Statistical Classification of Heat Illnesses*

992.0	Heatstroke and sunstroke (apoplexy, pyrexia, ictus solis, siriasis, thermoplegia)
992.1	Heat syncope (collapse)
992.2	Heat cramps
992.3	Heat exhaustion, anhydrotic (prostration due to water depletion)
992.4	Heat exhaustion (prostration due to salt and water depletion)
992.5	Heat exhaustion, unspecified (prostration not otherwise specified)
992.6	Heat fatigue, transient
992.7	Heat edema
992.8	Other heat effects
992.9	Unspecified

*Adapted with permission from the Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. Geneva, World Health Organization, 1977, p 535.

Heat Syncope

Even standing quietly in the heat before (or more commonly after) exercise results in an increase in venous volume in skin and limbs, dependent upon muscle contraction and venous valves to adequate cardiac filling pressure. If filling pressure and stroke volume decline rapidly, a fall in cardiac output and blood pressure will occur, resulting in syncope. The diagnosis of heat syncope is based on the observation of a short-term fainting episode in the absence of elevated rectal temperature. Recumbency, rest, avoidance of sudden or prolonged standing, and oral replacement of fluid/electrolyte deficits are adequate treatment. Heat syncope is typically categorized as a syndrome distinct from heat exhaustion (table 2).

Heat Exhaustion

Volume Depletion. Heat exhaustion is typically a problem of depleted volume of the body's circulating fluid or plasma.[2-4] Two forms of dehydration constitute the most widely recognized categories of heat exhaustion: salt depletion and water depletion. Dehydration due to salt depletion (low dietary NaCl, high losses of NaCl, or both) results in a loss of extracellular fluid and in reduced plasma volume, cardiac output, and blood pressure; it is neither characterized by thirst nor relieved by ingestion of salt-free fluids.

Dehydration primarily due to water deprivation or fluid loss is characterized by thirst and oliguria, and is relieved by the ingestion of water. Severe heat exhaustion due to salt depletion produces a form of peripheral vascular collapse that closely resembles traumatic shock because in this situation, plasma volume contributes one fourth of the extracellular deficit. Water depletion, with a comparable decline in total body water, does not produce peripheral vascular collapse because the plasma volume contributes only one twelfth of the total fluid deficit, and little or no protein leaves the vascular compartment.[2,5] Heat exhaustion due to water depletion is more likely to lead to heatstroke than is heat exhaustion due to salt depletion. Because of the similarities in symptoms, differentiating between these two forms of heat exhaustion may be difficult. Our observations made during laboratory and field studies[4] suggest that patients often have symptoms of moderate to severe salt-depletion heat exhaustion, yet are not clinically salt depleted. In fact we emphasized in a 1986 report[6] that pure forms of salt-depletion and water-depletion heat exhaustion are rare because body fluid losses (eg, diarrhea, vomitus,

sweat, urine) involve mixed water and salt losses. Reduced levels of urine and plasma sodium and chloride seem to be the only consistent diagnostic index.

Heat Cramps. Heat cramps are a frequent complication of heat exhaustion, but they sometimes occur as the only complaint, with minimal systemic symptoms. Hyponatremia and hypochloremia confirm a diagnosis of heat cramps. Leithead and Gunn[7] reported that the urine of 40 healthy field laborers contained 10 gm NaCl per liter of urine, while field laborers with heat cramps lost only 4 gm NaCl per liter. The laborers with heat cramps were conserving salt by decreasing urinary excretion, a symptom of a whole-body deficit. Similarly, Talbot[8] observed serum sodium levels ranging from 121 to 140 mEq/L (normal range, 135 to 145 mEq/L) in 32 patients with heat cramps.

We have previously described cases in which other conditions (eg, hyperventilation-induced tetany, gastrointestinal infections) have been mistaken for heat cramps.[3] Heat cramps in voluntary skeletal muscle affect only a few muscle bundles, and as one bundle relaxes, an adjacent bundle contracts for one to three minutes. This gives the impression that the cramp wanders over the affected muscle. Although the pain of severe heat cramps is excruciating, the following treatment is rapid and effective: intravenous (IV) saline (0.5 to 1.0 L normal saline) or 1% oral NaCl solution (two 10-grain salt tablets crushed in 1 L water).

A nonclassic form of heat exhaustion also has been reported[9]; it is characterized by hyperventilation, respiratory alkalosis, increased pH, tetany, carpopedal spasms, and abdominal cramps. This type of heat exhaustion is independent of lactic acidosis and salt/water depletion; it has been noted in unacclimatized soldiers who were involved in speed marching. Syncope may be observed, but the cause probably involves reduced cerebral blood flow due to hyperventilation rather than venous pooling. Treatment includes rest, cooling, and rebreathing of expired air.

Volume Repletion. Oral rehydration therapy with appropriate fluids is generally preferred in ambulatory patients who have no symptoms of central nervous system dysfunction and who are free of vomiting and diarrhea. On the other hand, because exercise-induced heat exhaustion is primarily a volume depletion problem, IV therapy results in rapid recovery. Highly motivated, otherwise healthy adult victims of heat exhaustion from intense competition or exertion may require up to 4 L of IV fluid. For example, the 1985 Boston Marathon took place on a warm day in April (75° F) at a time of year when few runners would be acclimatized to heat (in contrast, the average daily maximum temperature in Boston during April 1986 was 54.6° F). In the medical tent at the finish line, IV fluid was administered to 158 runners with heat exhaustion. Later it was estimated that 90% of these patients recovered and walked away from the tent within 15 to 20 minutes.[10] Similar cases of rapid recovery from heat exhaustion have been reported by military r[illegible]ics using IV therapy in Grenada and Germany. Furthermore, our review of the clinical literature indicates that there is no agreement on a preferred IV solution to use in the treatment of heat exhaustion.[3] However, theory suggests that a saline solution will provide a longer-lasting benefit for extracellular/intravascular fluid deficits than a glucose solution.[3]

Although heat exhaustion is a milder form of heat illness than is heatstroke, it is the most common form of heat illness observed in athletic and military populations.[11] The classic case of exercise-induced heat exhaustion with fluid/electrolyte depletion can be distinguished from heatstroke by (1) the degree of central nervous system derangement, (2) rectal temperature below 40° C (104° F), and (3) insignificant changes in serum enzymes (eg, lactate dehydrogenase, creatine phosphokinase, alanine aminotransferase, aspartate aminotransferase) for 48 hours. However, there is a small subgroup of heat-injury patients who have high rectal temperatures, hypotension and confusion; these individuals fall somewhere between heat exhaustion and heatstroke. When the diagnosis is in doubt, they should be treated for heatstroke, since this injury can be fatal.

Heatstroke and Hyperthermia

Costrini et al[11] and Hubbard[12] noted that the pathophysiology of heat exhaustion and heatstroke may be similar and hypothesized that they may represent a continuum of diseases rather than separate entities. However, it must be remembered that symptoms of heat exhaustion and heatstroke may occur independently of

one another. Experimental studies on rats provide some support for this hypothesis. We reported[13] that a temperature of 40.4° C represented a threshold hyperthermia, above which heatstroke mortalities occurred in exercised, heat-stressed rats. A mean (± SE) core temperature of 41.5° ± 0.1° C at exhaustion produced a 50% mortality rate within 24 hours. These results suggest a continuum, in that the probability of mortality seemed directly related to the core temperature at collapse. These findings also emphasize our observation that if victims of hypotensive heat injury are left unconscious and untreated, their condition may progress from severe heat exhaustion to heatstroke.

In our animal model[9] the longer the rats exercised, the higher their core temperature rose, and the more likely they were to incur a serious case of hyperthermia. This is analogous to human victims. These individuals—usually young, highly motivated, and healthy—are essentially unaware of the severity of their hyperthermia, in contrast to the more familiar sensations of fatigue or exhaustion.[14] We previously reported[15] that an Olympic marathoner produced metabolic heat in excess of 1,400 kcal per hour. Under conditions that limit heat dissipation, this rate of heat storage could have approximated 0.5° C per minute, and heatstroke levels of hyperthermia could have occurred within 10 to 12 minutes. The lack of pain and the apparent subtlety of symptoms of evolving hyperthermia often allow athletes who may be driven by pride and discipline to voluntarily increase exercise intensity during the latter stages of competition.

Cooling Strategies

During the medical emergency of heatstroke, mortality is closely related to the duration and intensity of hyperthermia. But how effective is the process of cooling heatstroke victims? Costrini et al[11] demonstrated that immersion of 13 exertional heatstroke patients (rectal temperature > 106° F) in a tub of ice and water, combined with massage of the extremities, resulted in a 100% survival rate. Although opponents of ice water immersion emphasize the negative aspects of intense cutaneous vasoconstriction in the cooling process, it must also be recognized that acute circulatory failure occurs in 80% of heatstroke deaths and that aggressive cooling

markedly decreases cardiovascular complications.[11,16]

In their 1959 review of methods of cooling hyperthermic subjects, Wyndham et al[17] strongly denounced cooling with ice water. Yet later findings from the same laboratory[18] indicated that between 1969 and 1980 the ratio of heatstroke fatalities to incidents rose among gold miners, despite a reduced incidence of heatstroke. It is relevant that the treatment of heatstroke did not include ice water immersion. Peripheral vasoconstriction via cold water immersion represents a physiologically pertinent means of restoring blood pressure. If vasoconstriction is induced before IV treatment, the risk of overzealous fluid administration—which can lead to pulmonary congestion or edema—may be avoided.

Since a delay in cooling heatstroke patients increases the risk of serious injury, military medics attempt to cool such casualties in the field as close to the point of collapse as possible. However, the amount of ice that would be needed to cool casualties as well as to provide cool drinking water represents an overwhelming logistic burden. We calculate that 37.1 kg (82 lb) of ice would be required to cool an 80-kg man from 45° to 37° C in a tub of water that has been equilibrated with an air temperature of 43° F. In practice,[11] up to 400 lb of ice has been used for each patient. Therefore, the development and use of small, mobile water chillers to provide water at 15° C both for cooling casualties and for drinking was a necessary compromise. In fact Magazanik et al[19] reported that hyperthermic dogs were cooled as effectively in 15° C water as in ice water. If both ice and chilled water are unavailable, IV fluid replacement is indicated. An additional benefit of IV therapy is that other compounds can be added rapidly to the vascular compartment.

We have examined a promising adjunct to IV therapy.[20] Taking advantage of the well-known cutaneous flush that is induced by niacin, we hypothesized that this flush would counteract vasoconstriction during cold water immersion, thereby promoting cooling of the body core. Important to a complete understanding of these data is the fact that the niacin-induced flush occurs with no alteration in blood pressure or heart rate at cool ambient temperatures (eg, 72° F). Our preliminary findings indicate that oral nicotinic acid resulted in lower core temperatures (35.2° to 36.6° C) than controls (36.7° to 37.3° C) during 90 minutes of water immersion. Additionally, body cooling was greater in 30° C water than in 25° or 28° C water, which confirms that shivering and vasoconstriction counteract net heat loss. The striking feature of this finding was the magnitude of body cooling in relatively temperate water (30° C), which induced little shivering. We suggest that some optimal combination of niacin and IV diazepam (to control shivering) might be used someday as an adjunct to enhance whole-body cooling, even in heatstroke victims immersed in temperate water.

Table 3. Hypothetical Characteristics of a Site of Cellular Heatstroke Injury

Same membrane structure as other cells
Are temperature-sensitive
Function is related to changes in cell volume
Function adapts during endurance training
Function adapts during the heat-acclimatization response
Function is related to heat tolerance and fatigue during exercise
Ability to generate heat
Structure and function may be irreversibly changed

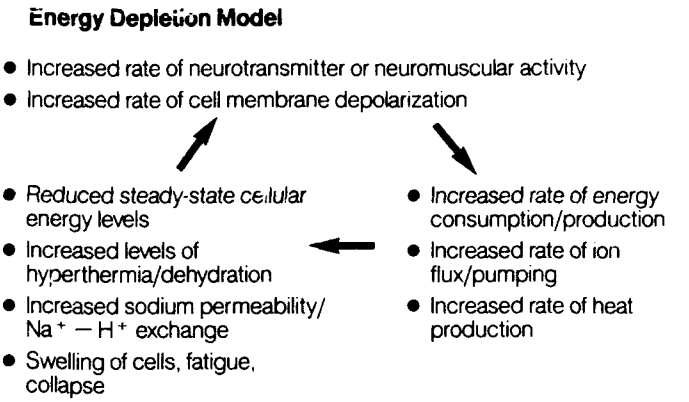

Figure 1. *In the the energy depletion model, key extracellular factors increase the permeability of the cell to sodium ions and stimulate the sodium pump, which burdens the cell with an additional energy drain. This model predicts that cellular/metabolic processes and deficits operate for some time after hyperthermia has subsided with cooling.*

The Pathophysiology of Heatstroke

We compiled a list[21] of hypothetical characteristics of a site of cellular heatstroke injury that would relate the physical effects of heat stress to the physiologic manifestations of heat strain (table 3). Cell membranes are in direct contact with hot blood, lymph, and extracellular fluid; they must function in some way to balance the destabilizing effects of extracellular changes on

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A few heat-injured patients have symptoms that place them somewhere between heat exhaustion and heatstroke; however, they should be treated for heatstroke, since this injury can be fatal.

the intracellular milieu. Basically, key extracellular factors increase the permeability of the cell to sodium ions and stimulate the sodium pump, which burdens the cell with an additional energy drain (the energy depletion model, figure 1).

Hyperthermia and exercise drive the sodium pump[21] in the following ways:

1. Hyperthermia increases intracellular acidity, which stimulates a Na^+-H^+ exchange.

2. Hyperthermia increases the kinetic energy and diffusion of ions in solution, which increases sodium permeability.

3. Heat storage is generally accompanied by hypohydration (sweating and voluntary dehydration), which increases sodium permeability by increasing the extracellular sodium concentration. This suggests that the hyperthermia of dehydration is due in part to a general increase in cellular heat production.

4. Hyperthermia increases the frequency of neural stimulation (nicotinic, cholinergic) necessary to maintain muscle force, which increases the sodium-potassium flux across nerves and stimulated muscles.

5. Hyperthermia and exercise produce regional ischemia (early splanchnic, late cerebral), which increases regional acidosis and Na^+ flux.

6. Heat storage and exercise increase muscarinic and nicotinic cholinergic stimulation autonomically and voluntarily, which increases Na^+ flux.

Sodium-potassium adenosine triphosphatase (ATPase) activity is regarded as the enzymatic equivalent of the sodium pump and accounts for a high proportion (20% to 45%) of the total energy used in resting cells.[21] Active sodium transport is present in all cells. The active transport of either sodium or potassium requires the presence of the other on the opposite side of the membrane and takes place against both concentration and electrical gradients. This active transport is tightly coupled and requires that one molecule of adenosine triphosphate (ATP) be hydrolyzed in order to return three sodium ions to the exterior of the cell in exchange for two potassium ions. The velocity of active transport depends on the concentrations of the cations at their respective binding sites and is remarkably sensitive to an excess of sodium ions inside the cell membrane. Because pumping activity increases approximately in proportion to the third power of the sodium concentration, a doubling of internal sodium concentration results in an eightfold increase in ATP hydrolysis. Thus any factor or condition that stimulates the flux of sodium into the cell will increase ATP use and heat production and will be an energy drain on the organism.

The Energy Depletion Model

The energy depletion model (figure 1) had its roots in two key observations:

1. There was an apparent paradox between the dogma that heat was the sole noxious agent precipitating heatstroke and the observation that morbidity and mortality are significantly higher associated with exercise-induced hyperthermia than with equivalent hyperthermia alone.[12]

2. Treadmill performance (with work done at a constant speed and grade in our nonsweating animal model) was significantly and inversely related to heating rate.[21] In other words, the heat stored in the cell adversely affects performance or increases fatigue. Administration of physostigmine or dinitrophenol to worsen the situa-

tion followed and extended the relationship.

The energy depletion model suggests that an exercise-induced thermal imbalance leads to an energy imbalance within the cells and requires the hypothetical creation of an ion-pumping motor (the sodium pump) fueled primarily by glycolysis[3] and a set of conditions to run it at high speed to the point of overload and damage. The hypothetical accelerator is the rate at which sodium leaks into cells. This leak rate is now seen to have significant autogenerating or positive feedback potential. We have diagrammed this dynamic relationship between rate of heat gain, increased membrane permeability, cellular energy depletion, and increased neurotransmitter activity as a cycle that leads to reduced heat tolerance during exercise and significant morbidity and mortality.

The outcome of this proposed pathophysiologic mechanism would depend on many factors, including the duration, intensity, and rate of heating as well as variations in regional and local circulation. The cascade undoubtedly begins with heat, is accelerated by acidity, and is gradually worsened by hypohydration. This hypothesis fits comfortably within the framework of our clinical experience and provides a clear, rational basis for the importance and urgency of cooling, which reduces an additional source of heat production (ie, sodium-potassium ATPase activity). This is also consistent with the recognition by neurosurgeons and cardiovascular surgeons that hypothermia provides clinical protection from circulatory arrest by lowering the basal metabolic rate. Cooling restricts Na^+ channels, delays energy depletion, delays K^+ efflux, and stabilizes the cell membrane.[22] The energy depletion model therefore supports the importance of body cooling as a primary form of treatment of heatstroke. **PSM**

Address correspondence to Roger W. Hubbard, PhD, US Army Research Institute of Environmental Medicine, Heat Research Division, Natick, MA 01760-5007.

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